Remarks

Claims 1-19, 21-22, and 77-80 are pending. Claims 20 and 23-49 have been cancelled. Claims 50-76 were withdrawn as being directed to a non-elected invention.

Rejection Under 35 U.S.C. § 103

Claims 1-19, 21, 22 and 77-80 were rejected under 35 U.S.C. § 103(a), as being unpatentable over Harris et al. (U.S. Patent No. 5,849,544) in view of Herrnstadt et al. (U.S. Patent No. 5,487,993). Applicants respectfully traverse this rejection.

Applicants submit the present rejection is based on misinterpretations of Harris et al. and of the claimed method. Harris et al. does not disclose what is alleged in the Office Action and, as a result, the combination of Harris et al. and Herrnstadt et al. do not disclose or suggest what is presently claimed. In addition, there is no teaching, motivation or suggestion to combine the teachings of Harris et al. and Herrnstadt et al. to achieve the subject matter of the current claims. These errors render the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness.

Applicants submit that, even considered together, Harris et al. and Herrnstadt et al. fail to disclose and suggest every feature of the claimed method. Applicants also submit that the Office Action's allegation that Harris et al. teaches primers with template-deficient nucleotides is incorrect. Harris et al. includes no such disclosure and cannot be interpreted as making such a disclosure. Applicants further submit that that the Office Action's allegation that Herrnstadt et al. teaches the use of template-deficient nucleotides in an oligonucleotide is incorrect. Herrnstadt et al. includes no such disclosure and cannot be interpreted as making such a disclosure.

In order for a reference or a combination of references to anticipate a claim or claims, "[f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally,

the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

Claims 1-19, 21, 22 and 77-80 are drawn to methods of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer, wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides. A careful reading of this claim language shows that the claim requires a template-deficient oligonucleotide that comprises one or more template deficient nucleotides. Template-deficient nucleotides are defined in the specification (see Specification page 11, lines 20-22) as nucleotides or nucleotide analogs that (when contained in a nucleic acid molecule) cannot serve as a template for nucleic acid synthesis. Whether a nucleotide is a template-deficient nucleotide can depends on the nucleic acid polymerase being used since certain types of nucleotides can be used as a template by some polymerases but not others (see Specification page 11, lines 27-30). In other words, whether a nucleotide is template-deficient is determined based on the nucleic acid polymerase being used in the nucleic acid amplification reaction (see Specification page 12, lines 2-3). While it is true that template-deficient nucleotides useful for making template-deficient oligonucleotides include biotinylated nucleotides, a nucleotide to which a biotin attached is not template deficient per se and the present application does not define biotinylated nucleotides as per se template-deficient.

Harris et al. describes a method for detecting a target nucleic acid sequence involving, in part, an amplification reaction whereby a detector tag is introduced into the amplified product. To introduce a detector tag into the amplified product, Harris et al. describes a primer oligodeoxynucleotide sequence to which a biotin group has been added at the 5' end (see diagram at bottom of column 3, to which Harris et al. refers at the top of column 4). Upon amplification of a target sequence, the primer is extended, such that the primer comprises a complementary sequence to the target. Harris et al. fails to disclose or suggest a template-deficient oligonucleotide that comprises one or more template-deficient nucleotides. As described above, template-deficient nucleotides are nucleotides or nucleotide analogs that (when

contained in a nucleic acid molecule) cannot serve as a template for nucleic acid synthesis. The functional effect is that a template-deficient nucleotide prevents synthesis of a nucleic acid strand complementary to a nucleic acid strand containing a template-deficient nucleotide. Merely adding a biotin group to the 5' end of a primer does not achieve this functional effect. As described above, the specification provides that whether a nucleotide is template-deficient is based on the nucleic acid polymerase being used in the nucleic acid amplification reaction. In other words, whether a primer with a biotin group on the 5' end is template deficient depends on the nucleic acid polymerase being used in the nucleic acid amplification reaction.

The Office Action appears to rely on the fact that the mere statement that a biotinylated nucleotide can be used to create template-deficient oligonucleotides, automatically establishes that any biotinylated oligonucleotide is a template-deficient nucleotide. This is simply incorrect and an overly broad interpretation of the specification. The Office Action alleges on page 6, lines 5-7 that "Given that a compound and its properties are inseperable, it stands to reason that the same compound, used in the same manner claimed, would exhibit the same properties." Such a statement exemplifies the fact that the Office Action has failed to appreciate a critical fact outlined above, namely that whether a nucleotide is template-deficient is determined based on the nucleic acid polymerase being used in the nucleic acid amplification reaction. The statement fails takes into consideration the relationship between the oligonucleotide and the polymerase being used. Nowhere in the Office Action is there any mention or direction of where in Harris et al. such a relationship is described or implied. Such an error renders the rejection legally flawed.

Furthermore, nowhere does Harris et al. indicate that the biotin at the 5' end of the primer would prevent the 5' nucleotide from serving as a template for replication. Further, nowhere in Harris et al. is there any mention of an oligonucleotide that contains a template-deficient nucleotide that would functionally inhibit synthesis of a nucleic acid strand complementary to the biotinylated primer disclosed by Harris et al. The biotin added to the primer of Harris et al. is merely for detection of the amplified product. Furthermore, nowhere in Harris et al. is there any mention of placing a detector tag (e.g. biotin) anywhere other than the 5' end of the primer. In addition, nowhere does Harris et al. indicate or draw any conclusions as to whether the nucleic

acid polymerase in conjunction with the biotinylated primer would cause the biotinylated nucleotide to meet the requirements of a template-deficient oligonucleotide. Thus, there is no disclosure of primers having template-deficient nucleotides, no disclosure of the function of template-deficient nucleotides, and no disclosure of the placement of template-deficient nucleotides such that they could have the required template-deficient effect. As such, Harris et al. fails to disclose or suggest a template-deficient oligonucleotide that comprises one or more template-deficient nucleotides.

Herrnstadt et al. was cited as teaching a method of conducting nucleic acid amplification using primers containing both complementary and non-complementary nucleotides. Although Herrnstadt et al. was not previously cited for disclosing template deficient oligonucleotides the current Office Action now alleges that Herrnstadt et al. does teach primers that meet the limitations of using template-deficient nucleotides in an oligonucleotide. The Office Action relies on column 11 of Herrnstadt et al. for allegedly teaching template-deficient nucleotides in an oligonucleotide. This is simply incorrect. The cited portion of Herrnstadt et al. is drawn to alternatives to labeled dNTPs. The use of the various labels are described as being used as part of the dNTPs used in primer extension reactions, not as part of the primers themselves (see Herrnstadt et al. column 11, lines 47-51). The "oligonucleotide" that results from the primer extension reaction is the "oligonucleotide" that comprises the label. This is not the same as what is claimed, namely a template-deficient oligonucleotide used as a primer.

Furthermore, the primers described by Herrnstadt et al. are "substantially" complementary to the different strands of each specific sequence to be synthesized or amplified (see Herrnstadt et al., col. 6, lines 46-48). The Herrnstadt et al. primers comprise stretches of complementary and non-complementary nucleotide sequences. Both the complementary and non-complementary sequences are amplified during the amplification process (see Herrnstadt et al. col. 6, lines 44-64). Applicants again direct the Examiner's attention to the definition of a template-deficient oligonucleotide as nucleotides or nucleotide analogs that (when contained in a nucleic acid molecule) cannot serve as a template for nucleic acid synthesis. All of the sequences of the Herrnstadt et al. primers are capable of, and in fact, serve as a template for nucleic acid

synthesis. Thus, the Herrnstadt et al. primers are not template-deficient. As such, Herrnstadt et al. fails to disclose template-deficient oligonucleotides.

In addition, there is no nexus in Herrnstadt et al. or Harris et al. between the non-complementary nucleotides of Herrnstadt et al. and the claimed template-deficient nucleotides. Accordingly, Herrnstadt et al. fails to provide the disclosure missing from Harris et al., and Harris et al. and Herrnstadt et al. together fail to disclose or suggest a template-deficient oligonucleotide that comprises one or more template-deficient nucleotides.

For at least these reasons, the claimed subject matter is not made obvious by Harris et al. and Herrnstadt et al., either alone or in combination.

The Office Action on page 4, lines 18-25 states that Herrnstadt et al. teaches that primers having as little as little as a 3 nucleotide exact match at the 3' end of the primer is capable of specifically initiating primer extension products, with Herrnstadt et al. citing Sommer et al. (Nucleic Acid Research, 17(16):6749 (1989)) for support. As applicants have previously argued (see pages 18-19 of the Supplemental Appeal Brief), this concept of a minimum exact nucleotide match at the 3' end of a primer is being misinterpreted and thus misused in relation to the claimed subject matter. What Sommer et al. actually discloses (and thus what Herrnstadt et al. discloses by reference) is not that three exactly complementary nucleotides at the 3' end will alone support efficient priming, but rather that, in a primer that otherwise has a sufficient number of nucleotides complementary to a target sequence to stabilize the primer/template hybrid (many more than three nucleotides in the primer extension reactions of Harris et al., Herrnstadt et al., and Sommer et al.), at least three of the complementary nucleotides in the primer must be at the 3' end of the primer for effective priming. This says nothing about how many complementary nucleotides are required (at the 3' end) to alone support efficient priming, which is the presently claimed requirement.

Sommer et al. merely suggests that successful priming can take place with three 3' nucleotides annealing to the template where a mismatch occurs immediately upstream. The primers of Sommer et al. have complementary nucleotides other than those at the 3' end that contribute to hybrid stability of the primers (see Table I in Sommer et al.). The present claims

explicitly require that only the nucleotides 3' of the template-deficient nucleotide closest to the 3' end be considered. The present claims require that these nucleotides alone must effectively prime. Sommer et al. does not suggest that this is possible for primers having only two or three complementary nucleotides.

Claims 1-19, 21, 22 and 77-80 require a template-deficient oligonucleotide that comprises one or more template deficient nucleotides. Neither, Harris et al. nor Herrnstadt et al., either alone or in combination, disclose or suggest such template-deficient oligonucleotide and so the cited publications fail to disclose or suggest every limitation of the present claims. Accordingly, and for all or the above reasons, the cited publications fail to make obvious claims 1-19, 21, 22 and 77-80.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No fees are believed due. However, the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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